dyskinesias, it would work with dyskinesias resulting from dopamine agonist therapy. However, no reason is given for believing this. There is no reason to assume that a treatment that is suitable for, say, tardive dyskinesia, mentioned in paragraph 5 of the official action would also be useful in treating dyskinesia related to dopamine agonist receptor therapy. Such therapy is commonly used in treatment of Parkinson's disease. However, again, it needs to be noted that we are concerned only with dyskinesia resulting from the treatment not with dyskinesia stemming from the underlying condition. The possibility of dopamine agonist therapy itself creating such dyskinesia is discussed on page 1 lines 22 to 27 of the present application as well as in the art cited by the Examiner. Hitherto, however, this has been regarded as being an inevitable long term consequence of dopamine agonist treatment that had to be endured in order to attain the other benefits of such treatment. Greenmayre "Pharmacological Pallidotomy With Glutamate Antagonist" Anals of Neurology 39(5) pp557 -558 (1996 (submitted with Information Disclosure Statement of January 27,1999) notes the development of dyskinesias in Parkinson's disease sufferers treated with levodopa. However, it states that "the pathophysiological basis of dyskinesias is understood poorly." (First sentence of paragraph bridging left and righ columns of page 557). This makes it difficult to predict how to treat these conditions and makes it unlikely that any particular approach could be obvious.

Nothing in the prior art points to the possibility of using an AMPA receptor antagonist to treat such dopamine agonist-induced dyskinesias. This was the issue considered previously with respect to the rejection over Klockgether which has now been withdrawn. However, it is equally or even more pertinent to the combinations of Arnold and Adams or Stella and Arnold and Adams on which the Examiner now relies.

Taking the first of these combinations, the examiner notes that Arnold et al teaches the use of an AMPA receptor antagonist to treat "neurological conditions" and that Adams teaches that dopamine agonist–induced dyskinesia is a neurological condition associated with Parkinson's disease. Where the Examiner errs, however, is from proceeding from these statements to an assertion that they make it *prima facie* obvious to use AMPA receptor antagonists for treatment of the particular condition specified in the applicants' claims. This is tantamount to saying "the common cold is an infectious disease, penicillin is used to treat infectious diseases therefore it is obvious to use penicillin to treat the common cold." Clearly it is not. One needs to consider in more detail what is known about both the specific condition to be treated and the compound proposed for such treatment. The neurological conditions listed in Arnold are the following: cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord trauma, head trauma, Alzheimer's Disease, Huntington's Chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, muscular spasms, migraine headaches, urinary incontinence, psychosis, convulsions, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage, opiate tolerance and withdrawal, ocular damage and retinopathy, idiopathic and drug-induced Parkinson's Disease, anxiety, emesis, brain edema, chronic pain, or tardive dyskinesia.(Column 3 lines 35 - 45). Many of these do not involve dyskinesia. Indeed the fact that despite the long list of conditions referred to, the only mention of a dyskinesia is tardive dyskinesia points away from the ise of such compounds for other types of dyskinesia since omission from such a long list implies that the author thought that the only dyskinesia that was susceptible to treatment with such compounds was tardive dyskinesia.

As discussed in response to previous actions, there is a clear distinction between the only dyskinesia mentioned in this list, tardive dyskinesia, and dyskinsesias associated with dopamine agonist therapy. In fact the Klogether et al reference considered previously in the prosecution of this application and Loschmann et al [Synergism of the AMPA-antagonist NBXQ and the NMDA-antagonist CPP with L-Dopa in Models of Parkinson's disease, J. Neural Transm. 3:203 - 213 (1991) - supplied with Supplemental Information Disclosure Statement filed on April 10, 2001] demonstrated that an AMPA receptor antagonist potentiates the effects of a dopamine agonist in animal models of bradykinesia, one of the neurological symptoms of Parkinson's disease. This data suggests that AMPA receptor antagonists and dopamine agonists act synergistically in producing behavioral responses.

To the contrary, the present applicants found that in the case of dopamine agonist-induced dyskinesias, AMPA receptor antagonists oppose the effect of dopamine agonists. Thus, the invention claimed in the present application of using an AMPA antagonist to inhibit dopamine agonist-induced dyskinesias was unexpected and contraindicated by the prior art. By taking a step in a direction that was contraindicated by the prior art, the applicants have clearly made a patentable invention which is not obvious over the combination of Arnold and Adams

The addition of the "Stella" reference (apparently Pappa and Chase Annals of Neurology 39: 574 - 578 (1996) does not change the proper conclusion drawn above from the simple combination of Arnold and Adams. The Pappa reference seems even less relevant since it relates to use of antagonists to a different type of glutamate receptor from those used in the present invention It is true that it teaches that antagonists to this particular receptor may have an effect in ameliorating levadopa-induced motor fluctuations in animal models of Parkinson's diseases. However, this does not point to use of antagonists for other receptors for any use whatsoever, let alone that claimed in the present application, particularly in view of the general degree of unpredictability in this field as noted above.

The Examiner states that, since AMPA and NMDA rceptors are subtypes of the same receptor, it is obvious that an AMPA receptor antagonist would also be useful in this regard. While it is true that AMPA and NMDA receptors are both ionotropic glutamate receptors, it is well know that these two receptors have clearly distinct physiologies (Seeburg, 1993; Dingledine et al., 1999 - copies supplied herewith). Consistent with this fact are the numerous reports in the literature that AMPA and NMDA receptor antagonists have very different physiological effects (Browne and McCulloch, 1994; Durmuller et al., 1994; Sheardown et al., 1993; Papa et al., 1993 - copies supplied herewith). Thus, the observation by Pappa and Chase that an NMDA receptor antagonist reduced dopamine agonist-induced dyskinesias would not have led to the deduction of the utility of an AMPA receptor antagonist to treat dopamine agonist-induced dyskinesias, since AMPA and NMDA receptors subserve distinct physiological functions and antagonists for the two receptor classes have distinct physiological effects. In fact, in light of the papers by Klockgether et al and Loschmann et al, the use of an AMPA receptor antagonist to treat dopamine agonist-induced dyskinesias was contraindicated until the applicants' invention. For the Examiner's convenience, the documents referred to in this paragraph are listed on Form PTO-1449 which is enclosed herewith.

It is therefore submitted that this application meets the requirements of 35 USC 103 and that the invention as claimed in each of the claims is not obvious over the references cited.

In response to the double patenting rejection, a terminal disclaimer is being submitted herewith to disclaim any term of a patent granted on the present application that might extend beyond the term of U.S. Patent 6136812.

In view of the foregoing it is believed that this application is now in order for allowance. An early action to this end is respectfully solicited. If the Examiner believes it would be useful to discuss this matter either personally or in a telephone interview, he is requested to let us know so that this can be arranged.

Respectfully submitted,

JOHN RICHARDS
c/o Ladas & Parry
26 West 61st Street
New York, NY 10023
Telephone No. 212-708-1915
Registration No. 31053